Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-3, 5, 6, 10-13, 35-37, 39-47 and 49 are pending in the application, with claims 1 and 39 being the independent claims. Claims 38 and 48 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. Claims 1, 10, 39, 44, 45 and 49 are sought to be amended. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Support for Amended Claims

Support for amended claims 1, 39, 45 and 49 can be found throughout the specification, for example, at page 18, lines 15-21. Support for amended claims 10 and 44 can be found throughout the specification, for example, at page 22, lines 7-12.

II. Objection to the Specification

The disclosure was objected to because, according to the Examiner, the status of the U.S. patent applications listed on pages 14 and 20-21 is missing. (*See* Paper No. 30, page 2.) Applicants respectfully request that this ground of objection be held in abeyance until the remaining issues in this application are resolved.

III. Objections to the Claims

A. Claim 1

Claim 1 was objected to because, according to the Examiner, "the phrase 'a DNA molecule of SEQ ID NO: 1' is grammatically improper." (Paper No. 30, page 2.) Applicants have replaced the phrase "a DNA molecule of SEQ ID NO:1" with "the DNA molecule of SEQ ID NO:1." Therefore, the objection to claim 1 is moot and should be withdrawn.

B. Claims 36 and 37

Claims 36 and 37 were objected to as being dependent upon a rejected base claim (claim 1). (*See* Paper No. 30, page 13.) As discussed below, Applicants respectfully traverse the rejection of claim 1. Accordingly, Applicants request that the objection to claims 36 and 37 as being dependent upon a rejected base claim be withdrawn.

C. Claim 38

According to the Examiner, "[c]laim 38 is a duplicate of claim 37 because SEQ ID NO: 1 only encodes SEQ ID NO: 2." (Paper No. 30, page 14.) Claim 38 has been cancelled, thereby rendering this objection moot.

D. Claim 48

Claim 48 was objected to under 37 C.F.R. § 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. (*See* Paper No. 30, page 14.) Claim 48 has been cancelled, thereby rendering this objection moot.

E. Claims 39 and 49

According to the Examiner, "[c]laim 49 is a duplicate of claim 39 because SEQ ID NO: 1 only encodes SEQ ID NO: 2 and nothing else." (Paper No. 30, page 14.) In accordance with the Examiner's suggestions, claim 39 has been amended to recite "a DNA molecule that encodes the amino acid sequence set forth in SEQ ID NO:2," and claim 49 has been amended to recite "wherein said DNA molecule comprises a DNA sequence having the nucleotide sequence set forth in SEQ ID NO:1." In view of these amendments, the objection to claims 39 and 49 is moot and should be withdrawn.

F. Claims 40-43

Claims 40-43 were objected to as being dependent upon an objected claim (claim 39). (*See* Paper No. 30, page 14.) As discussed above, claim 39 has been amended to accommodate the objection to claims 39 and 49. Therefore, the objection to claims 40-43, as being dependent on an objected claim, is likewise accommodated.

IV. Claim Rejections Under 35 U.S.C. § 112, First Paragraph

A. Written Description

Claims 1-3, 5, 6, 10-13 and 35 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. (*See* Paper No. 30, page 3.) Applicants respectfully traverse this rejection.

The basis of the rejection is the Examiner's assertion that "[t]he specification does not provide sufficient description of a genus of DNA molecules with 90% homology to SEQ ID NO: 1 that codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells." (Paper No. 30, pages 3-4.) For the reasons set forth in Applicants' previous responses, Applicants submit that the written description requirement is fully satisfied for the subject matter of claims 1-3, 5, 6, 10-13 and 35. (*See* Applicants' Amendment and Reply Under 37 C.F.R. § 1.111, filed on January 21, 2003, pages 6-9.)

To satisfy the written description requirement of 35 USC § 112, first paragraph, an Applicant must convey with reasonable clarity to those skilled in the art that, as of the effective filing date, the Applicant was in possession of the invention. *See Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). As made clear by the Federal Circuit, "[t]he written description requirement does not require the applicant 'to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.'" *Union Oil Co. of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989,997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000). In addition, not all functional descriptions of genetic material necessarily fail to meet the written description requirement; rather, "the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002); *See also, Moba, B.V. v. Diamond Automation, Inc.*, 2003 U.S. App. LEXIS 6285 at 31-32 (Fed. Cir. 2003).

A person of ordinary skill in the art would have recognized that Applicants, at the time the application was filed, were in possession of the invention insofar as it encompasses

DNA constructs which comprise the DNA molecule of SEQ ID NO: 1 or a DNA molecule which is at least 90% homologous thereto, wherein said DNA molecule is under control of a heterologous neuro-specific promoter, and wherein said DNA molecule codes for a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

First, the DNA constructs encompassed by and used in the practice of the claimed invention are not defined *solely* in terms of their function. Claim 1 states that the DNA constructs comprise the DNA molecule *of SEQ ID NO: 1* or a DNA molecule *which is at least 90% homologous thereto*. Thus, the claims include a structural definition of the DNA constructs.

Second, procedures for isolating nucleic acid molecules that are at least 90% homologous to SEQ ID NO:1 are described in the specification and are well-known in the art. (*See* specification at page 19, lines 3-15.) Moreover, assays are described in the specification for determining whether a DNA molecule encodes a protein having an activity of AD7c-NTP when over-expressed in neuronal cells. (*See* specification at page 20, lines 1-29, and at page 45, line 16 through page 46, line 26.)

The detail provided in the specification for obtaining DNA molecules that are at least 90% homologous to SEQ ID NO: 1 and for determining whether they encode proteins having an activity of AD7c-NTP when overexpressed in neuronal cells would indicate to persons of ordinary skill in the art that Applicants were in possession of the claimed invention. This conclusion is fully supported by the USPTO's "Synopsis of Application of Written Description Guidelines" and by the Federal Circuit's current interpretation and application of 35 U.S.C. § 112, first paragraph. (*See* Applicants' remarks set forth in the Amendment and Reply filed on July 9, 2002, pages 10-13.) Applicants therefore respectfully request that the

written description rejection of claims 1-3, 5, 6, 10-13 and 35 be reconsidered and withdrawn.

B. Enablement

Claims 1, 2, 3, 5, 6, 10-13, 35, and 44-47 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. (*See* Paper No. 30, pages 6-7.) Applicants respectfully traverse this rejection for the reasons set forth in the Amendment and Reply Under 37 C.F.R. § 1.111, filed on January 21, 2003, pages 10-13.

1. DNA Construct and Transformed Host Cell Claims

The rejection of claims 1-3, 5, 6 and 35, directed to DNA constructs and host cells transformed with the DNA constructs, is based on three general assertions. First, the Examiner stated that the specification "does not disclose which nucleotides of the claimed DNA molecule [are] considered essential for one skilled in the art to make a representative number of DNA molecules with 90% homology to SEQ ID NO: 1." (Paper No. 30, page 8.) Second, the Examiner asserted that "the specification does not provide sufficient guidance or factual evidence for one skilled in the art to determine without an undue amount of experimentation . . . if the nucleic acid sequence with at least 90 percent homology to SEQ ID NO: 1, would exhibit the same biological function of SEQ ID NO: 1." (Paper No. 30, page 8.) Third, the Examiner stated that "the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable."

(Paper No. 30, page 8.) Applicants respectfully submit that the foregoing reasons do not demonstrate that it would have required undue experimentation to make and use the claimed DNA constructs and transformed host cells.

In order to make and use the claimed DNA constructs and transformed host cells, a person of ordinary skill in the art would not need to know which nucleotides of SEQ ID NO:1 are "considered essential." Nor would a skilled artisan need to be able to predict protein activity from nucleotide sequence. Moreover, the specification provides ample guidance for determining whether a DNA molecule that is at least 90% homologous to SEQ ID NO:1 encodes a protein that has an activity of AD7c-NTP when over-expressed in neuronal cells.

At the time the present invention was made, persons of ordinary skill in the art could have easily obtained DNA molecules for use with the present invention by: (1) obtaining DNA molecules that are at least 90% homologous to SEQ ID NO:1, and (2) assaying the corresponding proteins for an activity of AD7c-NTP when over-expressed in neuronal cells. One of ordinary skill in the art would have been able to obtain DNA molecules that are at least 90% homologous to SEQ ID NO:1 using only routine methods in the art. (*See, e.g.*, specification at page 19, lines 3-15.) In addition, it would have required no more than routine experimentation to assay the corresponding proteins for an activity of AD7c-NTP when over-expressed in neuronal cells. The specification describes various methods for assaying AD7c-NTP activity. For example, transgenic animals can be made that over-express AD7c-NTP, and, once obtained, the transgenic animals may be analyzed for evidence of neuronal or neuritic abnormalities associated with Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas or glioblastomas. (*See* specification at page 20, lines 1-29.) Additionally, *in vitro* methods can be used which involve the overexpression of AD7c-NTP

in neuronal cells and the subsequent analysis for cellular characteristics of Alzheimer's disease, including apoptosis and neuritic sprouting. (*See* specification at page 46, lines 4-26.)

Since a person of ordinary skill in the art, based on the present specification, would have easily been able to obtain DNA molecules that are at least 90% homologous to SEQ ID NO:1 and assay the corresponding proteins for an activity of AD7c-NTP when over-expressed in neuronal cells, it cannot be concluded that obtaining DNA molecules for use with the present invention would involve undue experimentation.

In order to establish a *prima facie* case of lack of enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office. . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *See In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original). The Examiner has not presented any evidence or arguments indicating that the process of (1) obtaining DNA molecules that are at least 90% homologous to SEQ ID NO:1, and (2) assaying the corresponding proteins for an activity of AD7c-NTP when over-expressed in neuronal cells, would have involved undue experimentation. Thus, a *prima facie* case of non-enablement has not been established for the subject matter of claims 1-3, 5, 6 and 35.

2. Method Claims

The rejection of claims 10-13 and 44-47, directed to *in vitro* methods for screening a candidate drug that is potentially useful for the treatment or prevention of, *inter alia*, Alzheimer's disease, is based on three general assertions. First, the Examiner asserted that "[t]he specification does not teach how to distinguish true negatives from false negative[s] or true positives from false positives using the method contemplated in the claimed methods." (Paper No. 30, page 9.) This assertion is based on the notion that, since the DNA molecules used in the practice of the methods are under the control of a heterologous promoter, "[t]he suppression or prevention of expression of the protein coded by the DNA construct in b(i) would reflect interaction with the control sequence and result in false positives/false negatives." (Paper No. 30, page 10.) The second assertion upon which the rejection of the method claims is based is that "the specification does not teach how to distinguish an increase in degradation of the protein coded for by the DNA construct from a decrease [in] expression of the protein coded for by the DNA construct." (Paper No. 30, page 10.) The third assertion in support of the rejection is based on the supposed inability of a skilled artisan to "determine whether the mechanism caused by the candidate drug is the result of interacting with the promoter, the cDNA, or another protein in the cultured cells." (Paper No. 30, page 10.) As discussed below, these assertions do not support a *prima facie* case of lack of enablement.

The claimed methods comprise: (a) contacting a candidate drug with the host cell of claim 5 or 42, and (b) detecting at least one of the following: (i) the suppression or prevention of expression of the protein coded for by the DNA construct of said host cell; (ii) the increased degradation of the protein coded for by the DNA construct of said host cell; or (iii)

the reduction of frequency of at least one of neuritic sprouting, nerve cell death, degenerating neurons, neurofibrillary tangles, or irregular swollen neurites and axons in said host cell, wherein said host cell is a neuronal cell; due to the drug candidate compared to a control cell line which has not contacted the candidate drug.

The first assertion in support of the enablement rejection concerns the ability of one skilled in the art to identify "false negatives" and "false positives" in the context of (b)(i) of the method claims. The Examiner has apparently assumed that a drug that suppresses or prevents protein expression by interacting with the heterologous neuro-specific promoter would be a "false positive." This is not the case. The claims are directed to *in vitro* methods for screening a candidate drug that is potentially useful for the treatment of prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas. A drug that suppresses or prevents expression of the protein coded for by the DNA construct of the host cell by interfering with the *neuro-specific* promoter would be a "candidate drug that is potentially useful for the treatment of prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas." No evidence or scientifically sound arguments have been presented to suggest otherwise.

In addition, suppression or prevention of expression of the protein coded for by the DNA construct of the host cell can occur by mechanisms other than interaction with the promoter. A person of ordinary skill in the art would appreciate that suppression or prevention of expression of a protein can occur by, for example, degrading the mRNA that encodes the protein, reducing the stability of the mRNA, and interfering with the translation of the mRNA. Thus, in the context of the claimed methods, the suppressive effects of a drug on protein expression would identify the drug as a candidate that is potentially useful for the

treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas.

The second assertion to support the enablement rejection concerns the ability of one skilled in the art to distinguish an increase in protein degradation from a decrease in protein expression. There are numerous methods that were well known in the art at the time of the application that could have been used to distinguish (i) the suppression or prevention of expression of the protein coded for by the DNA construct of the host cell, from (ii) the increased degradation of the protein coded for by the DNA construct of the host cell. For example, a Northern blot could be used to assess levels of mRNA in the host cells after being contacted with the candidate drug. A Western blot (or other immunoassay) could be used to assess protein levels. A decrease in protein levels without a decrease in mRNA levels would indicate that the drug increased the degradation of the protein coded for by the DNA construct. A decrease in mRNA levels would indicate the suppression of expression of the protein coded for by the DNA construct. Northern and Western analyses for AD7c-NTP are exemplified in the specification at page 41, lines 1-28 (Example 5, Northern analysis), and at page 44, line 10 through page 45, line 15 (Example 7: Western analysis).

The third assertion to support the enablement rejection of the method claims is that:

> [t]he specification does not provide sufficient guidance or factual evidence for one skilled in the art to determine if detection of one of the following from step (b)(i)-(iii) is caused by the drug interacting with the non-coding sequence (e.g., promoter); with the AD7c-NTP cDNA, or independently with another gene product in the cultured cells.

(Paper No. 30, page 10.) In order to practice the claimed methods, however, it is unnecessary for one of ordinary skill in the art to determine the mechanism by which the drug causes at least one of (i), (ii), or (iii), as recited in the claims. The claims are directed to *in vitro*

methods for screening a candidate drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas. A candidate drug that causes at least one of (i), (ii), or (iii), regardless of what it interacts with or its mechanism of action, is a drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas. The drug may exert its effect directly or indirectly; either way, it is a drug that is potentially useful for the treatment or prevention of Alzheimer's disease, neuroectodermal tumors, malignant astrocytomas, or glioblastomas.

3. Summary

A person of ordinary skill in the art would have been able to make and use the DNA constructs encompassed by claims 1-3, 5, 6 and 35, and would have been able to practice the full scope of the methods encompassed by claims 10-13 and 44-47, without undue experimentation. The Examiner has not presented any specific evidence or sound scientific reasoning to indicate that it would have required more than routine experimentation to make, use and/or practice the subject matter of the claims. Therefore, the claims are fully enabled and a *prima facie* case of non-enablement has not been established. Accordingly, Applicants respectfully request that the enablement rejection of claims 1, 2, 3, 5, 6, 10-13, 35, and 44-47, be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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